Denali Therapeutics Announces New DNL343 (eIF2B Agonist) Phase 1b Data in ALS To Be Presented at the Upcoming AAN Annual Meeting

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- Data show that DNL343 is generally well-tolerated at doses that demonstrate robust inhibition of biomarkers associated with the integrated stress response (ISR)
- Clinical pharmacokinetic and ISR pharmacodynamic data, along with preclinical data, are consistent with extensive CNS distribution and support once-daily dosing
- Initiation of DNL343 regimen in the Phase 2/3 HEALEY ALS Platform Trial is expected in mid 2023

SOUTH SAN FRANCISCO, Calif., April 10, 2023 (GLOBE NEWSWIRE) -- Denali Therapeutics Inc. (Nasdaq: DNLI), a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier (BBB) for the treatment of neurodegenerative and lysosomal storage diseases, today announced that new data from the 28-day treatment period of the Phase 1b study of DNL343 in participants with amyotrophic lateral sclerosis (ALS) will be presented at the 75th Annual Meeting of the American Academy of Neurology (AAN), which will be held April 22-27, 2023, in Boston, Massachusetts. DNL343 is an investigational, small molecule eIF2B activator designed to cross the BBB with the potential of preventing or slowing ALS disease progression. The DNL343 abstract is available here on the AAN conference website. A PDF of the poster presentation will be made available on Denali's website under the Events section here after the AAN poster session begins at 11:45 a.m. EDT on April 25, 2023. As previously announced, DNL343 has been selected to enter the Phase 2/3 HEALEY ALS Platform Trial; Denali expects that recruiting will begin in mid 2023.

Denali previously announced initial interim Phase 1b results after 20 participants who had been randomized to receive DNL343 or placebo had completed the double-blind period of the study. The data demonstrated that once-daily oral dosing with DNL343 for 28 days was generally well-tolerated and was associated with extensive distribution in the cerebrospinal fluid as well as robust inhibition of biomarkers associated with the integrated stress response (ISR) as measured by *CHAC1* gene expression and ATF4 protein levels in blood samples from study participants. The Phase 1b pharmacokinetic profile along with preclinical *in vivo* data are consistent with extensive distribution of DNL343 in the central nervous system (CNS).

The upcoming presentation at AAN will include data from all 29 participants with ALS from the randomized, placebo-controlled, 28-day treatment period of the Phase 1b study. The results remain consistent with those previously reported as described above. Details of the presentation schedule are as follows:

Title: The Integrated Stress Response Is Modulated by eIF2B Agonist DNL343: Results from Phase 1 Healthy Subject and Phase 1b ALS Patient Studies (Poster #P8-010)
Session: Poster Session 8
Date: Tuesday, April 25, 2023
Time: 11:45 AM - 12:45 PM EDT

About DNL343 and the HEALEY ALS Platform Trial
Modulation of eIF2B activity with DNL343 is a novel and targeted investigational approach with first-in-class potential for the treatment of ALS. eIF2B is an intracellular protein complex that regulates protein synthesis and is required for neuronal health and function. When neurons experience stress, activation of the ISR pathway leads to suppression of eIF2B activity, resulting in impaired protein synthesis and formation of stress granules. Stress granules are thought to be a precursor of TDP-43 aggregation, which is a hallmark pathology in ALS. DNL343 is designed to activate eIF2B and thereby restore protein synthesis, disperse TDP-43 aggregates, and improve neuronal survival. DNL343 is an investigational therapeutic and has not been approved by any regulatory authority for any commercial use.

The HEALEY ALS Platform Trial is a large-scale collaborative effort made possible by contributions from patients and families, clinical trial sites, industry partners and research collaborators to evaluate multiple investigational therapies simultaneously with the goal of accelerating the development of potential new treatments for ALS. The platform trial is led by the Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital (MGH) in collaboration with the Northeast ALS Consortium (NEALS). Therapeutic candidates that enter the platform trial are chosen by a group of expert ALS scientists and members of the Healey & AMG Center.

About Denali Therapeutics
Denali Therapeutics is a biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier (BBB) for the treatment of neurodegenerative and lysosomal storage diseases. Denali pursues new treatments by rigorously assessing genetically validated targets, engineering delivery across the BBB and guiding development through biomarkers that demonstrate target and pathway engagement. Denali is based in South San Francisco. For additional information,

please visit www.denalitherapeutics.com.

Cautionary Note Regarding Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements expressed or implied in this press release include, but are not limited to, statements regarding plans, timelines and expectations related to DNL343, including the ongoing Phase 1b study, the initiation of patient recruitment for the Phase 2/3 study, the therapeutic potential benefit of modulating eIF2B, the therapeutic potential of DNL343 to prevent, slow, or treat ALS, and the commercial potential of DNL343; and the potential benefits of, likelihood of success of, and expectations related to Denali's collaboration with the HEALEY ALS Platform Trial. Actual results are subject to risks and uncertainties and may differ materially from those indicated by these forward-looking statements as a result of these risks and uncertainties, including but not limited to, risks related to: Denali's transition to a late stage clinical drug development company; Denali's and its partners' ability to initiate, enroll patients in, conduct, and complete its ongoing and future clinical trials, including the ongoing Phase 1b study and upcoming Phase 2/3 study of DNL343, on expected timelines; Denali's reliance on third parties for the manufacture and supply of its product candidates for clinical trials; the potential for clinical trial results of DNL343 to differ from preclinical, preliminary or expected results, including the initial Phase 1b results for DNL343; the risk of adverse events; risks related to Denali's collaborations; the risk that results from early clinical biomarker studies will not translate to clinical benefit in late clinical studies; the risk that DNL343 may not in the future receive regulatory approval as a treatment for ALS or other indications for which it is being developed; Denali's ability to obtain, maintain, or protect intellectual property rights related to its product candidates; implementation of Denali's strategic plans for its business, product candidates and BBB platform technology; and other risks. In light of these risks, uncertainties, and assumptions, the forward-looking statements in this press release are inherently uncertain and may not occur, and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements. Accordingly, you should not rely upon forward-looking statements as predictions of future events. Information regarding additional risks and uncertainties may be found in Denali's most recent Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on November 3, 2022, Denali's Annual Report on Form 10-K filed with the SEC on February 28, 2022, and Denali's future reports to be filed with the SEC. The forward-looking statements in this press release are based on information available to Denali as of the date hereof. Denali disclaims any obligation to update any forward-looking statements, except as required by law.

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